Lay Abstract

While the use of modern multimodality therapy has improved survival rates for many cancers, both adult and childhood sarcomas remain a formidable challenge in oncology. The survival of patients with relapsed, refractory, or metastatic disease remains dismal, and has not significantly improved with modern therapy. Similarly, metastatic neuroblastoma in childhood remains difficult to cure. There is no doubt that new types of therapies must be developed for these patients.

The idea of injecting tumors with infectious agents to elicit tumor shrinkage via then unknown mechanisms dates back at least a century. In the mid 1960's, virus injections were attempted but were abandoned due to low efficacy. With the advent of recombinant DNA techniques allowing manipulation of virus genomes and a markedly increased understanding of virus-cell and virus-host (immunologic) interactions, however, the field of oncolytic viruses is currently making what appears to be a sustained resurgence.

Oncolytic viruses are appealing as cancer therapeutics because they can be manipulated and they have multiple different anticancer mechanisms. First, they cause direct tumor cell death independent of conventional drug-resistance mechanisms. Second, they have the capacity for self-propagation, and therefore can potentially spread throughout a tumor and be active against bulky disease. Third, mutants can be constructed that have cancer selectivity either due to altered or missing viral protein functions or via the use of tissue-specific promoters. As a result, the therapeutic window of toxicity to target compared to normal cells can be manipulated and potentially may become quite large, suggesting viruses might be constructed that would have very few side-effects. Forth, oncolytic viruses can also be used to deliver therapeutic genes, so-called "armed" viruses, further expanding the potential antitumor mechanisms utilized by a single vector. Fifth, expression of some virus proteins actually sensitizes cells to apoptosis from chemotherapy and other agents. Sixth, the killing of virus-infected cells by natural killer cells (NK) or cytotoxic T lymphocytes (CTL), normal responses to viral infection, effectively amounts to an antitumor effect when the infected cell is a tumor cell. Seventh, virus infection and lysis of tumor cells may sensitize the host immune system to tumor-specific antigens that otherwise would not have been immunogenic, functioning as an *in situ* cancer vaccine. In summary, an oncolytic virus may potentially be useful not only as a "biologic surgery" for bulky disease but also as an immunotherapy.

In is conceivable that oncolytic viruses might be used both as a method of local tumor control, via direct intratumoral injection, and control of metastatic disease, via systemic administration. We believe it is important to first demonstrate safety and efficacy using the route of delivery most likely to be safe and effective, direct local administration, prior to studies of systemic delivery. Therefore, our protocol is important for bringing oncolytic viruses to cancer therapy in a careful, stepwise fashion. The inclusion of children is essential in order for this type of therapy to be tested on deadly diseases that are unique to pediatric oncology.